

REMARKS/ARGUMENTS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

Claims 12 and 25-32 were rejected under 35 USC § 112, second paragraph, as being indefinite. According to the Examiner, the claims do not clearly indicate how the step of contacting human blood with antibodies specific for CD4/CTLA-4 or CD25/CTLA-4 relates to the method of removing the regulatory T cells. In response, Applicants have amended main claim 12 to make clear that the embodiment claimed here involves removing the T cells by separating from human blood T cells that are bound to the antibodies. The amendment to claim 12 (and, therefore, also, claims 25-32) finds ample support throughout the specification, for example, in item G at page 10, lines 6-12; and in the Cell Isolation protocol at page 18, lines 24-28. Applicants do not believe that the amendment to claim 12 constitutes new matter. An early notice to that effect is earnestly solicited.

Claims 12 and 25-32 were rejected under 35 USC § 112, first paragraph, as being broader than the enabling disclosure. The Examiner finds a lack of enablement in connection with the claimed use of antibodies specifically binding to CTLA-4 to remove CD4⁺CD25⁺ T cells from human blood. In response, Applicants respectfully submit that the Examiner's understanding of the state of the art and of the teachings of the instant specification are not accurate, and, further, that the specification does, in fact, enable the practice of the full scope of the present claims.

The Examiner sets forth as an initial matter the fact that the claims are missing essential steps, those being how the CTLA-4 antibodies relate to the removal of the CD4⁺CD25⁺ T cells

from human blood. As to this initial matter, Applicants point out that main claim 12 has been amended above to make clear that the CD4⁺CD25⁺ T cells are removed from human blood by binding the CD4⁺CD25⁺ T cells to such antibodies.

The Examiner apparently anticipates this, because she then takes the positions that CD4⁺CD25⁺ T cells in human blood only express intracellular CTLA-4, and do not express surface CTLA-4, citing Jago et al. (2004); and that the instant specification on pages 11-12 discloses that CD4⁺CD25⁺ T cells in human blood do not express CTLA-4 at the surface. In response, Applicants respectfully submit that the Examiner's reading of the instant specification is clearly in error. First, the specification at page 11, lines 28-30, expressly teaches that "the CTLA-4 molecule (CD152) was already constitutively expressed (at high levels intracellularly, and at *low levels at the surface*) by the human CD4⁺CD25⁺ T cells * * * (emphasis added)." Consequently, it is simply incorrect that the instant specification on pages 11-12 teaches that CD4⁺CD25⁺ T cells in human blood do not express CTLA-4 at the surface.

Further, Applicants respectfully draw the Examiner's attention to Example 2 on page 21 of the instant specification, which also discusses surface expression of CTLA-4 on CD4⁺CD25⁺ T cells. The specification here expressly teaches that "[w]ithout prior stimulation, ie. *ex vivo* the CD25⁺ population already expressed high levels of intracellular, and *low levels of cell surface* CTLA-4 (CD152) (again, emphasis added)." Moreover, this statement is supported by the data in Figure 1B, which shows in the first row of the second column that 23% of CD4⁺CD25⁺ T cells were positive for surface expression of CTLA-4.

Given the fact that the use of antibodies specifically binding to surface markers to separate those cell populations (particularly from blood) has been known in the art for a long time; the fact that the specification discusses the separation of CD4⁺CD25⁺ T cells from human blood using antibodies specific for surface markers of those cells; and the fact that the specification additionally teaches that antibodies against CTLA-4 are useful in such endeavor, and further provides proof that CD4⁺CD25⁺ T cells express CTLA-4 on their surface, Applicants respectfully submit that the instant specification does, in fact, enable persons skilled in the art to remove CD4⁺CD25⁺ T cells from human blood by contacting the human blood with antibodies specifically binding to CTLA-4.

Claim 33 was rejected under 35 USC § 103(a) as being obvious over Koulis et al. ("Koulis"), *J. Allergy Clin. Immunol.*, S294-S295 (2001), in view of Read et al. ("Read"), *J. Exp. Med.*, 192: 295-302 (2000), and Leung et al. ("Leung"), *J. Biol. Chem.*, 270: 25107-25114 (1995). In response, Applicants respectfully submit that the cited combination of references fails to make out a *prima facie* case of the obviousness of claim 33.

According to *Manual of Patent Examining Procedure* ("MPEP") § 2143:

"To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest *all* the claim limitations (emphasis added)."

The Examiner takes the position that Koulis' PBMC population is "a population of CD4⁺ T cells from the blood," as recited in claim 33. In response, Applicants have amended claim 33 to make clear that what are isolated from the human blood are CD4⁺ T cells. Isolation of PBMC does not meet the terms of isolation of CD4⁺ T cells in the same way that a claim to "isolated CD4⁺ T cells" would not be anticipated by isolated PBMC. Consequently, the amendment above to claim 33 is believed to remove the possibility that the Examiner correctly reads Koulis' isolation of PBMC as reading on instant step (a).

In the cited combination of references, there is no teaching or suggestion to isolate CD4⁺ T cells, and then to isolate CD4⁺CD25⁺ T cells from the isolated CD4⁺ T cells. In other words, the cited combination of references does not teach or suggest carrying out both instant steps (a) and (b). Consequently, the cited combination of references fails to make out a *prima facie* case of the obviousness of claim 33 for this reason alone.

Further, the Examiner concedes that Read's teachings are limited to *mice*. The Examiner takes the position that a person having ordinary skill in the art, given Read, would have been motivated to test Koulis' T cells for the expression of CTLA-4 in order to determine if Koulis' T cells constitutively express CTLA-4 as their murine counterparts do. And, the Examiner finds a reasonable expectation of success in such testing since Leung teaches antibody reagents can be used to measure CTLA-4 expression in human T cells. A person having ordinary skill in the art would have had no reasonable *expectation* that human T cells should constitutively express CTLA-4 simply because their murine counterparts expressed CTLA-4 and, therefore, such person would have had no reasonable expectation that testing human T cells for constitutive expression of CTLA-4 should be successful. Indeed, there are significant immunological differences

between mice and humans. See, for example, Mestas et al., *J. Immunol.*, 172: 2731-2738 (2004), a copy of which is enclosed to the accompanying information disclosure statement. In view of the well known significant differences between mice and humans, a person having ordinary skill in the art would not have been reasonable to expect that human T cells should constitutively express CTLA-4 simply because their murine counterparts do.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,
NORRIS McLAUGHLIN & MARCUS, P.A.

By /Kurt G. Briscoe/
Kurt G. Briscoe
Attorney for Applicant(s)
Reg. No. 33,141
875 Third Avenue - 8th Floor
New York, New York 10022
Phone: (212) 808-0700
Fax: (212) 808-0844